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CLINICAL AND NEUROIMAGING ASPECTS OF NEUROLOGICAL SYNDROMES IN SYSTEMIC CONNECTIVE TISSUE DISEASES

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ABSTRACT

Systemic connective tissue diseases belong to a group of diseases that are characterized by the development of autoimmune processes against antigens of almost all organs and tissues of the body, which is combined with the formation of autoantibodies with organ-nonspecific properties. Autoimmune processes carry out information exchange between the neuroendocrine and immune systems, with the main role played by autoantibodies to hormones, mediators and their receptors [3,6].

INTRODUCTION

Data have been obtained on the neurogenic regulation of immune functions and their disorders, while at the same time, immunocompetent cells and their mediators can affect the function of the central nervous system (CNS) according to the principle of neuroimmunomodulation. It has been shown that the entire central and peripheral nervous system has the property of neurosecretion. The influence of the immune and nervous systems on each other is realized through the receptor structures of cells, the interaction of which creates “receptor-receptor” bonds and thus organizes the molecular mechanism for the joint operation of both systems. The functioning of cells and signaling information are provided by mediators and neurotransmitters in both systems; information is exchanged between the nervous and immune systems using cytokines, steroids, and neuropeptides [1, 2, 3].

Thus, the commonality and interconnection of the nervous and immune systems, the similarity between their structures and functions, and the development of a new direction in modern immunology, neuroimmunology, have been proved [3, 4]. A wide range of neurological syndromes in autoimmune systemic diseases allows us to consider them as model systems for studying the pathogenetic role of immune mechanisms of damage to the central and peripheral nervous system [5]. Potential targets for autoimmune aggression can be various antigens of the nervous tissue, including myelin, including those associated with glycoprotein, and its main protein, gangliosides, protein of neuronal cell nuclei, and others [6]. Thus, target antigens in neurolupus are represented by neuronal tissue antigens, ribosomal P-protein, rDNA, small nuclear ribonucleoprotein, and anionic phospholipids in antiphospholipid syndrome, which causes a wide range of neurological symptoms in this pathology [7, 8].

According to various authors, the frequency of lesions of the nervous system in rheumatic diseases (RD) ranges from 40% to 70% or more, if mental syndromes and headaches are taken

into account. Neurological syndromes are included in the classification criteria for systemic vasculitis published by the American College of Rheumatology in 1990, in the diagnostic and activity criteria for systemic lupus erythematosus (SLE), as well as in a number of other diagnostic criteria, in particular polyarteritis nodosa in children. Neurological disorders in RD require differential diagnosis and the appointment of adequate treatment jointly by a rheumatologist and a neurologist.

A study conducted by N.P. Shilkina et al. [5], included 229 patients with various forms of RD, among whom 110 suffered from systemic connective tissue diseases: 88 patients with SLE, 22 with SJS, and 119 with systemic vasculitis, including 21 with thromboangiitis obliterans, 27 with polyarteritis nodosa, 32 with nonspecific aortoarteritis, 15 hemorrhagic vasculitis, 2 Wegener's granulomatosis and 22 other forms. A detailed neurological examination, ultrasound transcranial dopplerography of cerebral vessels, rheoencephalography, computed and magnetic resonance imaging of the brain, electroencephalography, and immune status were performed. In most patients, the disease debuted with skin (50.6%), musculoskeletal (35.4%) and vascular (27.1%) syndromes. Organ lesions at the onset were registered in 7% of patients, arterial hypertension syndrome - in 5.2%, fever - in 7.0%, hematological disorders - in 7.9%; neurological disorders (mono- and polyneuropathy and encephalomyelopolyradiculoneuritis syndrome) - in 12.2%. The onset of the disease with damage to the peripheral nervous system was especially characteristic of polyarteritis nodosa and was observed in 30% of patients. With lesions at the onset of CNS disease, cephalgic (10.5%) and vestibular (6.3%) syndromes were observed (more often with nonspecific aortoarteritis). CNS involvement was present in 96 (41.9%) patients and was especially pronounced in SLE, nonspecific aortoarteritis, and polyarteritis nodosa. Cerebrovascular pathology was dominant in the clinical picture of the disease in 34.7% of patients. Sometimes a variety of symptoms of CNS damage developed long before the appearance of a polysyndromic picture of the disease. The main syndromes in cerebrovascular pathology were the following syndromes: cephalgic (82%), asthenic (76%), vestibular-atactic (80%), pyramidal (74%), vegetative-vascular insufficiency (69%), dissomnic (79%) and basal - meningeal (37%), hypothalamic dysfunction (34.7%). This neurological symptomatology was often combined with symptoms of cerebral vascular insufficiency, which were combined with the syndrome of dyscirculatory encephalopathy I (11%), II (26.4%) or III (8%) degree [5].

The following features of neurological pathology in patients with systemic RD have been identified [16,3]:

• polymorphism of the clinical picture, due to a combination of neurological and somatic disorders, especially in patients with motor disorders due to rheumatic damage to muscles and joints;

• multiple and multilevel damage to the nervous system, accompanied by the development of mono- and polyneuropathy, myelopathy and encephalopathy, often due to multifocal brain damage;

• high incidence of neurological disorders at a young age (the first cerebrovascular accident in patients with SLE and APS often occurs before the age of 25);

• rapid and significant regression of acute neurological symptoms under the influence of GCs and cytostatics and the absence of such during traditional neurological treatment;

• the possibility of partial or complete regression of neurological and mental disorders in patients with long-term remission of RD (the most noticeable regression of neurological symptoms is observed with a short duration of the disease, especially after a single exacerbation).

According to Motovilov A.A. et al. the course of neurological pathology in most cases is associated with periods of exacerbation and remission of the underlying disease. In this case, an acute, relapsing or chronic course of neurological disorders can be observed. However, the development of neurological disorders does not always depend on the activity of systemic RD. In particular, with the formed symptomatic arterial hypertension, the development of acute cerebral disorders during the period of compensation of the underlying disease is possible [8,14]. The basis of the systematics of neurological and psychopathological manifestations proposed by Yu.V. Grachev, a topical sign was put, according to which three groups of neurological forms and syndromes caused by damage to the brain, spinal cord and peripheral nervous system were identified. Neurological manifestations of systemic RD usually represent a combination of so-called central and peripheral neurological disorders [5].

In SLE, the diagnostic criteria for neurological lesions include convulsions or psychoses. CNS damage is mainly due to vascular pathology, which includes vasculopathy, thrombosis, true vasculitis, infarcts, and hemorrhages [7]. In the cerebrospinal fluid, antineuronal antibodies are detected, an increase in the protein level, an increase in the cellular composition is determined. Different types of convulsive seizures are described: large, small, according to the type of temporal lobe epilepsy, as well as hyperkinesis. With CNS lupus, there is a migraine-type headache that is resistant to analgesics, but responds to treatment with glucocorticosteroids. Cranial nerve palsies are usually accompanied by ophthalmoplegia, cerebellar and pyramidal symptoms, and nystagmus. There are visual disturbances, transient disorders of cerebral circulation. Acute transverse myelitis is rare and has a poor prognosis. Mental syndromes are diverse and are characterized by affective, organic brain or schizophrenia-like manifestations [9, 10].

Antiphospholipid syndrome has also been described within SLE. This syndrome includes: recurrent arterial or venous thrombosis, recurrent miscarriage and thrombocytopenia and additional features: livedo reticularis, neurological manifestations: chorea, epilepsy, migraine headache, cerebrovascular accident and dementia due to multiple infarcts, chronic leg ulcers, Coombs-positive hemolytic anemia, valvular heart disease and serological markers - antiphospholipid antibodies, which include anticardiolipin antibodies IgG and IgM and lupus anticoagulant [11].

In systemic scleroderma (SS), the neurological syndrome is mainly represented by polyneuritic manifestations associated with vascular changes and fibrous processes in the connective tissue. Polyarteritis nodosa is characterized by multiple mononeuritis, Wegener's granulomatosis is characterized by asymmetric polyneuropathy, and nonspecific aortoarteritis is characterized by dyscirculatory encephalopathy and cerebrovascular accidents [3].

Cerebrovascular pathology was dominant in the clinical picture of the disease in 34.7% of patients, and sometimes various symptoms of CNS damage developed long before the appearance of a polysyndromic picture of the disease. The main clinical manifestations of cerebrovascular pathology included: cephalgic (82%), asthenic (76%), vestibular-atactic (80%),

pyramidal (74%) syndromes, vegetative-vascular insufficiency syndrome (69%), dyssomnic (79%) and basal membrane (37%), hypopotalamic dysfunction (34.7%) [3.16].

The described neurological symptoms were often combined with symptoms of cerebral vascular insufficiency, which were combined with the syndrome of discirculatory encephalopathy of 1 (11%), 2 (26.4%) or 3 (8%) degrees. Transient cerebrovascular accidents occurred in 7.8% of patients [11].

Hypothalamic dysfunction in patients with RD was manifested by polymorphic neuroendocrine disorders, impaired thermoregulation, mainly by the type of paroxysmal central hyperthermia, insomnia, and pathology of the psycho-emotional sphere [9].

When using MRI and/or CT methods, a change in the ventricular system was revealed in the form of its expansion or deformation and/or expansion of the subarachnoid space, as well as focal lesions of various brain structures, atrophy of the brain substance and craniovertebral anomalies. Signs of external, internal or combined hydrocephalus were noted in all nosological forms. Focal changes in the brain substance included hyperdense zones, hypodense zones with or without edema, single or multiple [17].

In the study of the vascular system and cerebral circulation, an increase in vascular tone, a hypertonic and dyscirculatory type of blood circulation according to rheoencephalography (REG) and an increase in the linear velocity of blood flow in the middle cerebral artery were reliably observed. Patients with CNS involvement differed in electroencephalography: they were characterized by diffuse pathological changes, the presence of alpha rhythm disorganization, dysrhythmias, and paroxysmal activity [15,17].

Focal lesions of the brain differed in the localization of the process depending on the nosological form.

Among patients with RD, cerebrovasculitis (CV) occurred in 28.3% of patients. The diagnosis of CV was made upon detection of focal neurological symptoms, changes in the fundus, decreased vision, signs of cerebrovascular accident, as well as the results of CT and nuclear magnetic resonance imaging (NMRI), which revealed external and internal hydrocephalus, focal changes in cortex and subcortical substance. At the same time, over time, the number of foci of any localization in the brain increased. Magnetic resonance angiographic (MRA) study revealed multiple segmental irregularities of the vascular wall, circular or eccentric stenoses and dilatation of small and medium intracranial arteries with the formation of aneurysms, and blood flow disturbances. The revealed decrease in the intensity of the MRA signal against the background of an increase in the activity of the rheumatic process indicated the presence of CV [6].

Immunological markers of CV were considered antibodies to native DNA, IgG antibodies to cardiolipin (aCL) and IgM-CL, antineutrophil cytoplasmic antibodies (ANCA), and to a lesser extent RF and lupus anticoagulant (LA). There were clinical and immunological correlations with neurological manifestations [4].

Isolated (primary) CV was characterized by the detection of symptoms of CNS involvement and such signs as headache, convulsions, meningeal syndrome, acute progressive encephalopathy without signs of extracranial or systemic vasculitis, mental syndromes, dementia, progressive decline in intelligence, strokes, visual impairment, nystagmus. More often, periventricular lesions were detected in the first year of the disease [8].

A number of patients consulted an ophthalmologist due to visual impairment, up to amaurosis, the presence of uveitis, ischemic neuritis. Retinal angiopathy occurred in 41% of these patients, phlebopathy - in 14%, retinovasculitis - in 6%, angiospasm - in 13%, angiosclerosis - in 18%.
Polyneuritic syndrome occurred in the vast majority of patients (96.7%) in the form of sensory, sensory-motor polyneuropathy or in combination with CNS lesions, with EPN and EMRN syndrome. In SJS, OT, and HB, forms in the form of sensitive or sensory-motor polyneuropathy prevailed, while in SLE and NAA, forms with combined damage to the peripheral NS (PNS) and CNS — EPN and EMRN syndromes — prevailed. With OT and NAA, a distinct dissociation of the severity of polyneuropathy along the body axis was noted, and with OT, the symptoms were more distinct in the legs, with NAA, in the hands. In general, asymmetric polyneuropathy occurred in 19.2% of patients, reaching a maximum in UP (59.3%) [4,8].
The pathology of NS in RD often determines the prognosis, the clinical picture of the disease and the quality of life of patients, and also requires the mandatory combined use of basic anti-inflammatory therapy, angio- and neuroprotectors.
Treatment consists of several stages: rapid suppression of the immune response at the onset of the disease and during its exacerbations (induction of remission); long-term maintenance therapy with immunosuppressants, in doses sufficient to achieve clinical and laboratory remission of the disease; determining the degree of damage to organs or body systems and their correction, carrying out subsequent rehabilitation measures [16].
The most effective and less toxic schemes for the use of immunosuppressive drugs, the ways of their administration, and the inclusion in the complex treatment of patients of drugs that improve microcirculation and/or affect the rheological properties of blood are being determined.
The appointment of angioprotectors and post-syndrome therapy is indicated.
Given the high proportion of neurological pathology, patients with RD should undergo a comprehensive clinical and instrumental neurological examination already at an early stage of the pathological process. The diagnosis of RD and complex therapy with glucocorticosteroids, immunosuppressants, angioprotectors, and neuroprotectors contribute to the correction of CNS and PNS disorders [11].

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